

## Teaching Case

# First case of Merkel cell carcinoma in a young patient with Sweet syndrome

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## Introduction

Merkel cell carcinoma (MCC) is a rare cutaneous malignancy with a high propensity for regional lymph node metastasis and recurrence. Acute febrile neutrophilic dermatosis (Sweet syndrome) is an acute inflammatory skin eruption that is commonly associated with hematologic malignancies, but cases in association with solid tumors have also been reported.<sup>1</sup> We present the first case of a 49-year-old female who experienced an acute flare up of Sweet syndrome during her initial diagnosis and subsequent treatment for MCC.

## Case report

A 49-year-old Caucasian female presented with bilateral erythematous patches and edematous plaques on the cheek in June 2012. She had been experiencing the eruption for more than 19 years. Previous skin biopsies, as well as the skin biopsy of the cheek performed at the time of consultation, demonstrated a diffuse, bandlike infiltrate of neutrophils in the dermis consistent with diagnosis of Sweet syndrome (Fig 1A, B and Fig 2). She was started on a regimen of topical steroids in addition to

occasional prednisone tapers starting at 40 mg. Her subsequent lesions were also transiently responsive to intralesional triamcinolone injections, but typically failed to respond to colchicine and nonsteroidal anti-inflammatory drugs.

One month later, the patient presented with a new nodule on her left cheek. Skin biopsy demonstrated neoplastic cells displaying basaloid morphologic features with vesicular nuclei, minimal cytoplasm, and indistinct nucleoli suggestive of neuroendocrine carcinoma. Immunohistochemistry was positive for cytokeratin 20 and negative for S-100 protein, CD-45, cytokeratin 7, and transcription factor-1 within the neoplastic cells. Based on these results, the patient was diagnosed with MCC occurring in a background of chronic Sweet syndrome; to our knowledge, this is the first concurrence of these disorders reported in the medical literature (Fig 3).

After review in multidisciplinary tumor board, patient underwent wide local excision and sentinel lymph node biopsy from the left parotid and left cervical nodal basin, which was negative for metastatic disease. She was staged as T1 N0 M0, stage IA, with subsequent positron emission tomography scans demonstrating no scintigraphic evidence of residual or recurrent disease. She then received 50 Gy external beam radiation using electrons at 2 Gy per fraction over 5 weeks to the primary site only (Fig 4), without radiation to the lymphatic tissue, based on multidisciplinary consensus from 2 different academic institutions. The patient completed radiation treatments 2 months after initial diagnosis and tolerated the treatment well. She experienced expected side effects including

Conflicts of interest: None.

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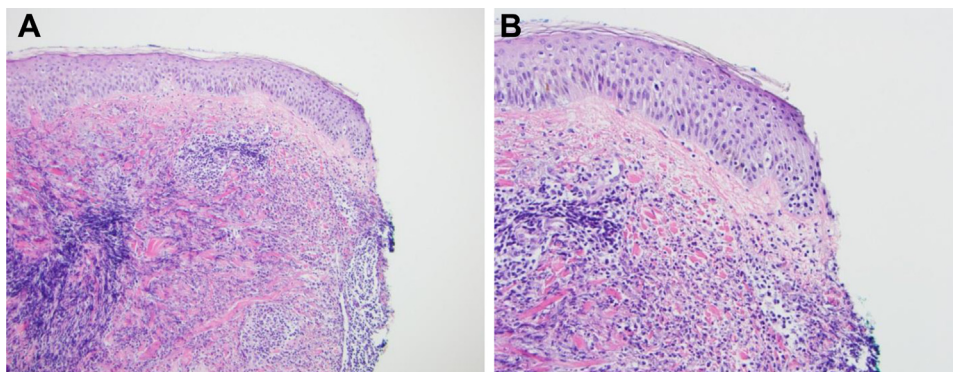
**Figure 1** Bilateral erythematous patches and edematous plaques consistent with clinical diagnosis of Sweet syndrome before treatment. (A, B) Photographs taken at time of computed tomography simulation with scar wire and head mask. (C) One month post-treatment. (D) Six months posttreatment.

mild erythema, intermittent mucosal erosions, and desquamation of the irradiated field (acute toxicity was grade 2, which resolved within 4 weeks after completion of radiation therapy). Restaging positron emission tomography and clinical examination 2 months out from treatment completion showed no evidence of MCC, and she was declared to be in complete remission. She has followed up regularly and has not experienced any recurrence of MCC (Fig 1C, D). The patient initially had a dramatic improvement in her Sweet syndrome lesions, which were located in the irradiated field, during the treatment course. She then had recurrence of Sweet syndrome with 2 lesions within the irradiated field at 7 weeks after radiation therapy, which responded to topical therapy. She is currently well-managed with dapsone 100 mg daily and topical clobetasol for both symptomatic and

clinical control of her cutaneous lesions. The patient is also on intermittent prednisone 40 mg tapers during acute exacerbations of symptoms.

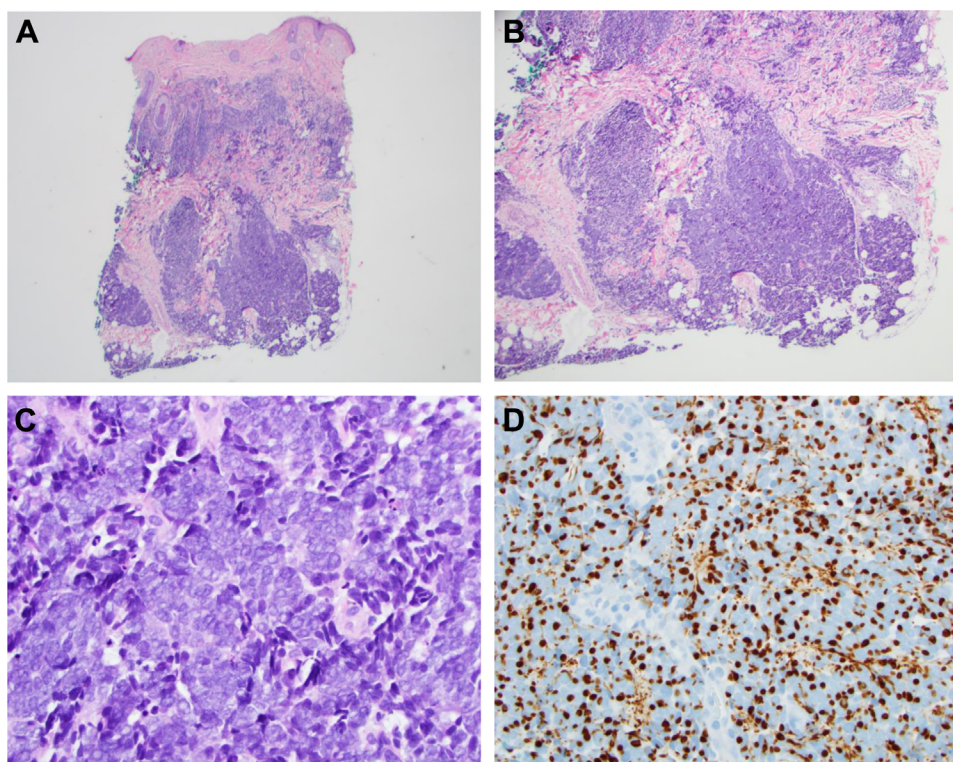
## Discussion

MCC is a rare cutaneous malignancy that typically presents as a rapidly growing, nonpainful, flesh-colored or bluish-red, dermal nodule or cystic lesion. Initial clinical impression is often that of benign lesions, which can result in significant delays in biopsy and diagnosis. Treatment for MCC with a negative lymph node biopsy involves surgical excision with either postoperative radiation therapy or observation of the primary site. For MCC with biopsy-positive nodes, a multidisciplinary tumor



**Figure 2** Punch biopsy of lesional skin at (A) 100× and (B) 200× demonstrating a diffuse, bandlike infiltrate composed primarily of neutrophils within the superficial dermis with associated papillary dermal edema consistent with Sweet syndrome.

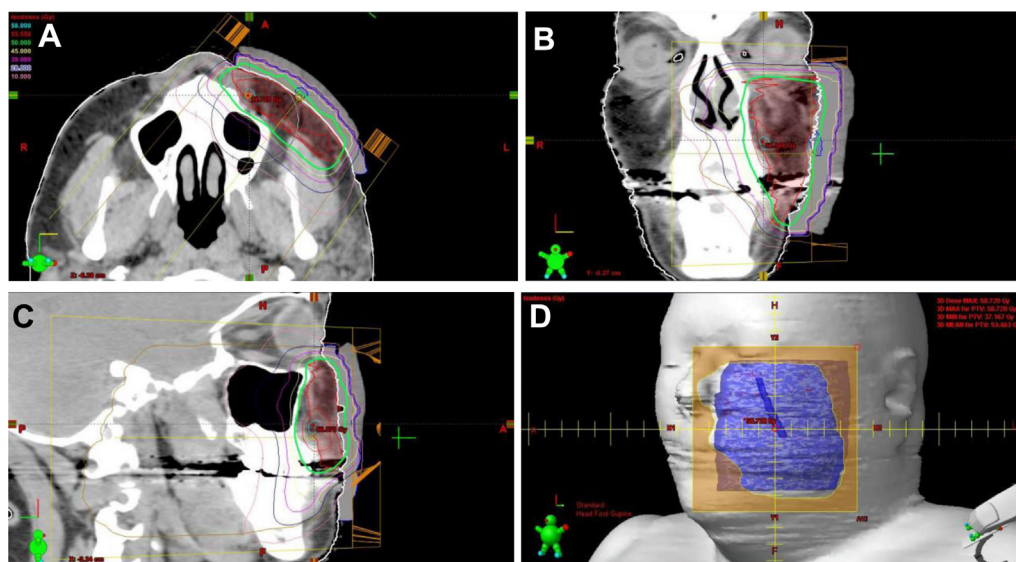




**Figure 3** Merkel cell carcinoma skin biopsy demonstrating nodules and sheets of basophilic tumor cells in the dermis and superficial subcutis at (A) 20 $\times$  magnification and (B) 40 $\times$  magnification. (C) 400 $\times$  magnification demonstrating vesicular nuclei with small nucleoli and scant cytoplasm. (D) Immunohistochemistry for cytokeratin 20 is positive in tumor cells seen at 400 $\times$  magnification.

board treatment plan should be considered involving a combination of lymph node dissection, radiation therapy, or adjuvant chemotherapy. Adjuvant radiation therapy to

primary site is generally recommended for all excision sites, despite mixed opinions about its benefits. National Comprehensive Cancer Network guidelines suggest a



**Figure 4** Patient was simulated in the supine position with arms down, using a customized thermoplastic facemask for immobilization. The planning treatment volume (PTV) was defined as the surgical scar plus a customized 3-cm margin, 2 cm near the eye. We used an internal eye shield to reduce dosage to critical eye structures. The left cheek PTV was treated using a 9 MeV electrons, en face technique 44 Gy at 2 Gy per fraction, prescribed to the 90% isodose using a 0.5-cm tissue equivalent bolus. An additional 6 Gy of 2 Gy per fraction without bolus was boost was given for a total dose of 50 Gy. Heterogeneity correction was used for planning. The prescribed radiation treatment was completed. (A) Axial view. (B) Coronal view. (C) Sagittal. (D) 3-dimensional rendering.

total radiation dosing of 50 to 56 Gy for negative resection margins, 56 to 60 Gy for microscopic resection margins, and 60 to 66 Gy for gross or unresectable margins.<sup>2</sup> Harrington and Kwan showed 5 year overall survival rates of 57%, 68%, and 39% for stage I, II, and III disease, respectively, using definitive radiation therapy on primary and/or nodal disease.<sup>3</sup> We have typically offered adjuvant radiation therapy to the primary in almost all cases given our own clinical experience with observation resulting in increased local recurrence.

Sweet syndrome is an inflammatory skin condition characterized by tender, erythematous, edematous skin lesions often affecting the head and neck.<sup>1</sup> The disease predominantly affects women and classically arises between the ages of 30 to 60 years of age.<sup>4</sup> There are 3 subtypes of Sweet syndrome. Classical Sweet syndrome is induced by inflammatory conditions such as infections and autoimmune disorders. Drug-induced Sweet syndrome also represents a significant portion of cases; a common culprit is granulocyte colony stimulating factor. Finally, malignancy-induced Sweet syndrome accounts for 10% to 20% of cases overall.<sup>1</sup> The skin condition is predominantly associated with hematological cancers (42% had acute myelogenous leukemia)<sup>5,6</sup>; solid tumors are less likely to be associated with Sweet syndrome. Topical and systemic corticosteroids are the cornerstone of management for Sweet syndrome.<sup>5</sup> Nonsteroidal anti-inflammatory drugs such as colchicine, potassium iodide, and dapsone have also been reported as efficacious.

There have been reports of Sweet syndrome arising in association with other cutaneous malignancies, including melanoma.<sup>7</sup> However, our case is the first reported association of Sweet syndrome with MCC reported in the medical literature. Our patient's presentation is unique for several reasons. First, she was diagnosed with the malignancy at a very young age; MCC usually occurs in older males with a history of extensive sun exposure.<sup>4</sup> Second, MCC is a highly immunogenic condition that is associated with other malignancies and an immunosuppressed state. The patient had no other pertinent medical history beyond a diagnosis of Sweet syndrome, and there were no medical conditions that would have increased her risk for MCC. Her relatively young age and lack of comorbidities may account for her good prognosis because MCC is traditionally an extremely aggressive disease with a 5-year disease-specific survival rate of 64% and a median overall survival duration of only 31 months.<sup>4,8</sup>

The manifestation of Sweet syndrome in this patient is also unique given the relative lack of knowledge regarding the pathophysiology of the disease. Specifically, the treatment of our patient's MCC did not involve any use of chemotherapy, thus ruling out drug-induced Sweet syndrome. In addition, she did not have any prior infections or autoimmune conditions that would meet criteria for classical Sweet syndrome. Although it is

known that nearly two-thirds of malignancy associated Sweet syndrome patients develop the syndrome before or concurrently with the diagnosis of the malignancy,<sup>1</sup> the diagnosis of Sweet syndrome in the patient occurred years before the diagnosis of MCC. Thus, any causal relationship between Sweet syndrome and MCC cannot be demonstrated. However, it is possible that the immunogenic changes caused by the cancer further disrupted autoinflammatory regulation in an already susceptible patient, the results of which manifested as an acute flare up of Sweet syndrome in the month before the diagnosis of MCC.

Finally, radiation therapy has been associated with many dermatologic side effects, the most common of which include benign dermatoses such as bullous pemphigoid, pemphigus vulgaris, and morphea.<sup>9,10</sup> There have even been reports of Sweet syndrome directly caused by radiation therapy.<sup>11,12</sup> It is important to recognize that radiation can cause direct inflammatory changes at the site of treatment, a pertinent consideration in patients with existing autoimmune skin conditions. Many radiation oncologists are hesitant to treat patients with scleroderma or systemic lupus erythematosus, conditions associated with a dysregulated immune system that have characteristic skin findings.<sup>13</sup> Given that reports of patients with Sweet syndrome requiring radiation therapy are sparse and the pathogenesis of the disease is autoimmune, it is logical to question the safety of radiation therapy in these cases as well. The initial regression of Sweet syndrome during and after radiation therapy, as well as the lack of significant radiation-induced toxicity in our patient, provides some reassurance for Sweet syndrome patients needing radiation therapy for the management of their malignancies.

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